

01-08-12 Preliminary Draft Comments from Clean Air Scientific Advisory Committee (CASAC) Ozone Review Panel. These preliminary pre-meeting comments are from individual members of the Panel and do not represent CASAC consensus comments nor EPA policy. Do not cite or quote.

**Preliminary Comments from Dr. Jack Harkema on**  
**EPA's Integrated Science Assessment for Ozone and Related Photochemical Oxidants**  
**(Second External Review Draft – September 2011)**

**Comments on Chapter 6: Integrated Health Effects of Short-Term Ozone Exposure**

**General Comments:**

In general, the overall format for this chapter is appropriate and the text is clearly written. The authors have thoroughly reviewed the recent literature and have included the most pertinent recent studies since 2006. There are areas of redundancy, however, in this chapter and in Chapter 7 that need to be eliminated.

In some sections of this chapter, the authors spend too much time rehashing details of studies previous to 2006. Emphasis should be placed more on significant recent novel findings and their relevance to the bottom-line conclusions of short-term ozone exposure's impact on specific health effects.

Not all of the sections follow the same format. The chapter would be improved with a consistent format of presentation that includes: 1) brief presentation of the major conclusions of the previous 2006 AQCD (summarizing tables of past studies could be used); 2) focused discussions on the major studies since 2006 that have contributed new and important information to the area (references may be made to previous important studies, but only when necessary); and 4) an overall summary/conclusion paragraph(s) that synthesizes and critically evaluates the relevance/impact of these studies on the subject area.

There are a few references to studies "In Press." These should be eliminated from the discussion.

**Specific Comments:**

6.1. The introductory paragraph is well crafted and clearly and concisely written. It nicely sets the stage for the reader.

6.2. Respiratory Effects. The conclusions from 2006 AQCD are well summarized.

**6.2.1 Controlled Human Exposure**

p.6-5. Good explanation of the need for FA control exposures. The authors may want to also discuss the possible impact of ambient O<sub>3</sub> exposure history prior to controlled O<sub>3</sub> exposures and whether or not most studies address this issue.

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Figure 6-1, p.6-7. The statistical significance of FEV1 decrements at each ozone concentration should be indicated in both graphs.

p.6-8, line 19. Since there are numerous abbreviations throughout this chapter, the authors may consider replacing “S-W” with “square-wave” throughout this section.

p.6-9, line 5. The authors may want to address what contribution each exposure scenario (triangular, square wave) makes to better understand the health effects of ambient exposure.

p.6-10, last paragraph. Clinical significance of a 6% decrease in FEV1 should be discussed here or elsewhere in this chapter (e.g., end of first paragraph on 6-11).

p.6-14, lines 20-21. Here the authors reference a decrement of FEV greater than 10% as an abnormal response. Does that imply that lower ozone-induced decrements are not clinically relevant?

p. 6-11, last paragraph. End this paragraph with a concluding statement on the clinical implication of O3-induced changes in small airways and ventilation distribution compared to the changes in large airways.

p. 6-15. At the end of the first paragraph, the authors should present some suggested biological reasons why COPD patients appear to be less sensitive to ozone exposures.

p. 6-15, Responses in Individuals to Pre-Existing Disease. Authors should provide the range of exposure concentrations and exposure scenarios used in these studies.

p.6-17. Factors Modifying Responsiveness to Ozone. In this section, it would be helpful to provide subtitles introducing the factors being discussed.

Very little new information is being presented in this section. This section should be shortened by presenting more concise statements on the major findings prior to 2006 and highlighting those from more recent studies.

p. 6-23,-24. In this summary, the authors should point out that few or no recent studies have been done in this area. Most of the information provided in this summary is based on studies prior to 2006.

#### 6.2.1.2. Epidemiology

A lot of the discussion focuses on studies prior to 2006 that was presented in the previous AQCD. The authors may want to consider shortening the descriptions from past studies and highlighting the more recent studies.

6.2.1.3 and 6.2.2.2 “Toxicology.” The titles are the same for both sections. Differences in the content of the sections should be designated somehow in the titles (e.g., 6.2.2.2 “Animal Toxicology”)

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The sections on Toxicology appear to follow a different presentation format than the other sections in this Chapter. Authors of this section should try to use the format used by others (see general comments). The toxicology sections could be shortened by providing more of a summary of previous findings prior to 2006 and providing more focus on the recent studies.

p.6-60, line 22. Do not include “In Press” studies.

6.2.3.3. Toxicology. Title could be changed to “Toxicology: Airway Inflammation.”

p.6-84. Respiratory Symptoms and Medication Use  
Some areas are redundant with previous sections.

p.6-102 The authors may want to reconsider changing the section titles to “Tracheobronchial Defense: Mucociliary Clearance “ and “Centriacinar Defense: Transport Mechanisms.”

6.2.5.4 Infection and Adaptive Immunity

Animal studies in this section are well written and concentrate on recent studies since the last AQCD (2006).

p.6-141, line 2. Reference needs parentheses.

6.2.9. Summary and Causal Determination p.6-137. Summary and Causal Determination of Respiratory Effects is very well written.

6.3 Cardiovascular Effects. P.6-143. This section of the Chapter is well presented with the most interesting new studies. The overall presentation of this section may be interpreted by some as demonstrating more than just a “suggested” causal relationship between short-term O<sub>3</sub> exposure and cardiovascular health effects.

Summary statements should be provided for all of the subsections under the cardiovascular effects.

p.6-175. In the Summary of Epidemiological Studies, the authors may want to expand upon the statement that there is consistent positive association found between O<sub>3</sub> and cardiovascular mortality.

6.3.3 Toxicology

p. 6-17, lines 1-13. It should be noted that the decrease in heart rate (bradycardia) and mean arterial pressure demonstrated in rats (Watkinson et al.) most likely is due to the trigeminocardiac reflex (or diving reflex), the most powerful autonomic reflex known in mammals, including humans. This reflex has been described for exposures to other inhaled nasal irritants. Interestingly, Peel et al. (Environ Health Perspect 2011) found robust associations of 8-hour maximum ambient ozone concentrations with bradycardia events among infants prescribed home cardiorespiratory monitors. This lends relevance to the cardiovascular toxicology found in the rat studies by Watkinson et al.

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p.6-177, 6.3.3.2. Recent CV Toxicology Studies  
line 17. The strain of mice should be specified.

6.3.3.2, p.6-177. It is not clear what CV effects of O<sub>3</sub>, besides mitochondrial DNA damage, were measured in the monkeys.

Table 6-39, p.6-182. The Perepu et al. study (2010) is a subchronic study and may be more appropriate in Chapter 7.

p. 6-184. The summary of the CV effects section is very well written. The suggested causative conclusion, however, appears somewhat conservative based on the results of the more recent studies. Most of the short-term exposure studies, though much more limited than those examining respiratory health effects, do demonstrate ozone-induced CV effects.

## **Comments on Chapter 7: Integrated Health Effects of Long-Term Ozone Exposure**

### **General Comments:**

In general, the overall format for this chapter is appropriate and the text is clearly written. The authors have thoroughly reviewed the recent literature and have included the most pertinent recent studies since 2006. There are some areas of redundancy with those in Chapter 6.

There are a few references to studies “In Press.” These should be eliminated from the discussion.

### **Specific Comments:**

7.1. Clear and concise introductory paragraph.

p.7-9, line 26. Should not include studies “In Press.”

p.7-17, section 7.2.3(Pulmonary Structure and Function) needs a summary paragraph highlighting the relevance of the new findings from recent studies.

p.7-30. Last paragraph should also include findings from recent nonhuman primate studies that examine the structure/function effects of ozone on house dust mite-induced allergic airway disease (e.g., Plopper et al., 2007; Joad JP, 2008), or refer to these studies that are discussed later in the chapter (p.7-59).

p.7-30. A table of the recent toxicology studies would be helpful.

p.7-35. A brief summary of the major new findings and their relevance should conclude the section on Cardiovascular Toxicology.

p.7-36. line 12. “In Press” references should not be included.

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p.7-37. Though the number of studies conducted in this area are more limited than those investigating respiratory effects, the data appears consistent that there is a causal relationship between long-term ozone exposure and CV effects.

p.7-61. Some of the exposure studies in the Laterality section, 7.4.9.1, are only for 6 days and are not long-term as defined by the authors (a month or greater). These studies could be included in Chapter 6.  
p. 7-63, 7.4.9.3. The lengths of the exposures under Sleep Aberrations are not specified.

p. 7.67, 7.4.10.5. Recent study by Peel et al. (Environ Health Perspect 2011; see comment above) may have relevance to ozone and SIDS.